

Antiphospholipid syndrome – magnifying glass of medicine

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Abstract: With a sense of unease we have recently learned about an intended limitation in internal medicine training for physicians qualifying for sub-specialities combined with administrative decisions practically limiting professional activity of internists only to hospital wards. Meanwhile, thorough training in internal medicine not only allows the physician to diagnose and treat the majority of medical patients, but is also indispensable in dealing deal with complicated clinical syndromes which fall outside smaller medical sub-specialities. Antiphospholipid syndrome may serve as a good example.

Key words: antiphospholipid antibodies, antiphospholipid syndrome, systemic lupus erythematosus, thrombosis

At present we are witnessing an ongoing discussion about the requirement for specialization in internal medicine by physicians who want to pursue a professional carrier in narrow specialties originating from internal medicine. The discussion is fueled, in a sense, by the administrative decision to eliminate medical outpatient clinics, which limits internal medicine to a hospital specialty. Nevertheless progress in medicine continuously confirms the priceless value of physician's ability to form a broader picture based on patient complains, symptoms and results. Antiphospholipid syndrome is an example (one out of many) confirming this opinion.

We can look at the history of antiphospholipid syndrome in two ways. Its laboratory features are tightly bound to the simple, nonspecific VDRL test, described in the forties which detects syphilis reagin. Cardiolipin, a negatively charged phospholipid from the bovine heart served as an antigen in this test. It rapidly turned out that many subjects tested falsely positive and some of them suffered from systemic lupus erythematosus (SLE). In the fifties an anticoagulant had been described in the blood of SLE patients [1]; hence it has later coined name – lupus anticoagulant.

Different observations determine the clinician's view. By 1954 an anticoagulant was reported in a woman with a history of seven spontaneous abortions [2]. In 1963 Bowie et al. pointed out to the paradoxical coexistence of such an anticoagulant with thrombotic complications [3].

In the beginning of the eighties a test was introduced with the use of cardiolipin (first radioimmunoassay, then enzyme-linked immunoassay) to detect anticardiolipin antibodies. Many patients with SLE and these antibodies suffered from thrombotic complications [4]. At this point research groups from Great Britain, USA and France were coining a term: antiphospholipid syndrome, secondary to SLE. As early as in 1980 professor Boffa described an association of lupus anticoagulant with recurrent spontaneous abortions and thrombosis in a woman with no symptoms of SLE; here a term of primary antiphospholipid syndrome appears. The first diagnostic criteria, characteristic for antiphospholipid syndrome, are proposed which include the coexistence of clinical symptoms (recurrent abortions, venous and arterial thrombosis, thrombocytopenia) and laboratory features (the presence of lupus anticoagulant and/or anticardiolipin antibodies) [5]. Finally, in 1990 three research groups (from Europe, Japan and Australia) simultaneously reported that a protein – β_2 -glycoprotein I (β_2 -GPI) – is required for binding of antiphospholipid antibodies to negatively charged phospholipids [6].

Now let's take a 15-year long jump in time, to the year 2005, or even to the beginning of 2006, and present a contemporary opinion on this fascinating syndrome. The principal symptom – vascular thrombosis – is an immune-mediated phenomenon. Antiphospholipid syndrome is probably the most frequently occurring autoimmune disease. Antiphospholipid antibodies (aPL) do not only interfere with the hemostatic system reactions mediated by negatively charged phospholipids but they also activate the endothelium [7]. In fact these antibodies are not directed against phospholipids but against domain I of β_2 -GPI. For this reason thrombotic complications are most closely associated with the presence of β_2 -GPI-dependent lupus anticoagulant and anti- β_2 -GPI antibodies [8]. Thrombosis: arterial, most often manifested as

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Table. Updated classification criteria for the antiphospholipid syndrome

Clinical criteria	Laboratory criteria*
1. Vascular thrombosis Venous**, arterial or small vessel thrombosis; one or more objectively confirmed clinical episodes; without significant evidence of inflammation	1. Lupus anticoagulant – detected according to ISTH guidelines
2. Pregnancy morbidity a. One or more unexplained deaths of a morphologically normal fetus ≥ 10 wks. of gestation, or b. One or more premature births < 34 wks. of gestation because of: I. eclampsia or severe preeclampsia; II. recognized features of placental insufficiency c. Three or more unexplained consecutive spontaneous abortions < 10 wks. of gestation (maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded)	2. Anticardiolipin antibodies – of IgG and/or IgM isotype, present in medium or high titer (> 40 GPL, or MPL; or $>$ the 99 percentile), measured by a standardized ELISA 3. Anti- β_2 -GPI antibody – of IgG and/or IgM isotype; in titer $>$ 99 percentile; measured by a standardized ELISA Each of the above mentioned tests must be positive on two or more occasions at least 12 wks. apart

Antiphospholipid antibody syndrome (APS) is present if at least one of the clinical criteria and one of the laboratory criteria are met.

Classification of APS should be avoided if less than 12 weeks or more than 5 years separate the positive aPL test and the clinical manifestation.

* – it is advised to classify APS patients into one of the following categories: I. – more than one laboratory criteria present (any combination); IIa – LA present alone; IIb – aCL antibody present alone; IIc – anti- β_2 -GPI antibody present alone.

** – superficial vein thrombosis is not included in the clinical criteria

ischemic stroke; venous. mainly deep venous thrombosis of the lower extremities and affecting small vessels of many organs and tissues are most strongly associated and characteristic for this syndrome. Together with obstetric complications (mainly recurrent spontaneous abortions) those symptoms were included among clinical classification criteria proposed in Sapporo in 1998 and published a year later [9]. The presence of lupus anticoagulant and anticardiolipin antibodies in medium or high titer were included among the laboratory criteria. But many other symptoms were passed over in silence. For this reason these criteria has been updated recently during an experts' meeting in Sydney (2004) and published at the beginning of 2006 [10]. Leaving out many details important only for research purposes, let's concentrate on the changes important for the clinician (table).

Among serological criteria antibodies against β_2 -GPI were added, at levels exceeding the 99 percentile of the healthy population. Two positive results are still mandatory, but now at least 12 weeks apart instead of six.

The most crucial changes affected clinical criteria and symptoms. The symptoms mentioned earlier remained, because of their sensitivity and specificity for the syndrome. However, a close attention is paid to their conformity with generally accepted definitions (e.g., pre-eclampsia, eclampsia, placental insufficiency, objective conformation of thrombosis). When the presence of aPL is confirmed, coronary artery disease, intracardiac thrombi, transient ischemic attacks (TIA) and histologically proven aPL-associated nephropathy, are all considered thrombosis related to antiphospholipid syndrome or its equivalent.

An emphasis was placed on some clinical features quite frequent in APS but not specific for the syndrome. These include: a/ cardiac valve disease, b/ livedo reticularis, and c/ thrombocytopenia. New terms were coined: aPL-associated cardiac valve disease, aPL-associated livedo reticularis, aPL-associated thrombocytopenia (see also aPL-associated nephropathy, mentioned above), and specific requirements for their diagnosis were given. The exact clinical significance of such symptoms associated with APL but not fulfilling definite criteria for APS deserves further study.

Also the role of some other antiphospholipid antibodies (e.g., antiphosphatidylserine, antiphosphatidylethanolamine, antiprothrombin) awaits further clarification; providing they are not associated with classic APL antibodies.

Finally, it was advised against using the terms "primary" or "secondary" APS. Firstly because laboratory and clinical features are the same and secondly because in many patients with an initially primary form of disease a fully blown systemic lupus erythematosus eventually develops.

Antiphospholipid syndrome is not a trivial problem. Ischemic stroke at a young age, recurrent obstetrical complications, and last but not least, the authentic risk of pulmonary embolism and the development postthrombotic syndrome deserve decisive action. This is based mainly on effective antithrombotic treatment. Today it includes oral anticoagulants (INR 2,0–3,0; in special situations – 3,5) and in pregnant women – heparins, mainly low molecular weight products.

Patients with APS may seek help from various physicians representing the internal medicine sub-specialties: rheumato-

logists, hematologists, cardiologists, angiologists, clinical immunologists, but also: neurologists, obstetricians, dermatologists or vascular surgeons. The syndrome is just one of many examples, a pretext if one prefers, to emphasize how important is a thorough training in internal medicine to properly diagnose and effectively treat these and similar patients. For a good internist fragmentary pieces of information converge like in a magnifying glass. It is him who picks these pieces together to offer the patient the best possible care. In this way the physician becomes an example of such a right and desirable relation in medicine: one patient – one doctor. It should be our ambition to provide such training to our fellow-physicians, regardless of the motivation and necessity in achieving further steps in medical specialties. I am deeply convinced to this idea.

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